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The Synthesis and Fungicidal Activity of 2-Substituted 1-Azol-1-ylmethyl-6-arylidenecyclohexanols

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Abstract: A number of substituted 2,2-dimethyl-6-arylidene-1-triazol-1-ylmethylcyclohexanols and 2,2-dimethyl-6-arylidene-1-imidazol-1-ylmethylcyclohexanols were prepared from 2-methylcyclohexanone in four steps: Claisen–Schmidt condensation with substituted benzaldehydes, methylation of the resulting 2-methyl-6-benzylidenecyclohexanones, conversion to the oxiranes by interaction with dimethylsulfonium methylide and reaction of the oxiranes with triazole or imidazole. The compounds obtained were tested for antifungal activity against five phytopathogenic fungi of different taxonomic classes. EC_{50} values were determined for all compounds. Structure–activity relationships are discussed in broad terms. Some of triazolymethyl-substituted cyclohexanols obtained are more active than triadimenol.

Key words: 2,2-dimethyl-6-arylidenecyclohexanones, 8-arylidene-4,4-dimethyl-1-oxaspiro[2.5]octane, 2-substituted 6-arylidene-1-azolylmethyl-cyclohexanols, azole fungicides, lanosterol, structure–activity relationship.

1 INTRODUCTION

The biochemical site of action of the fungicidal azoles is the oxidative transformation of lanosterol by the P-450 mixed function oxidase in fungal cells. This haem protein binds tetracyclic steroid molecules, inserting one oxygen atom into a CH bond of the C-14 methyl group.[1,2] Inhibitors of lanosterol oxidation must fit into the target site of the enzyme in a similar way to the natural substrate, which contains a *gem*-dimethylated cyclohexanol fragment, and it is likely that the high antifungal activity of triadimenol or tebuconazole is based on the similarity of *tert*-butyl groups in these compounds to this important element of the lanosterol structure.

2 EXPERIMENTAL

2.1 Synthetic methods

The synthetic routes employed are outlined in Fig. 1 and a list of the compounds obtained appears in Table 1. The 2-substituted-6-arylidenecyclohexanones (**2**) were prepared by condensation of substituted cyclohexanones with different aromatic aldehydes, according to the

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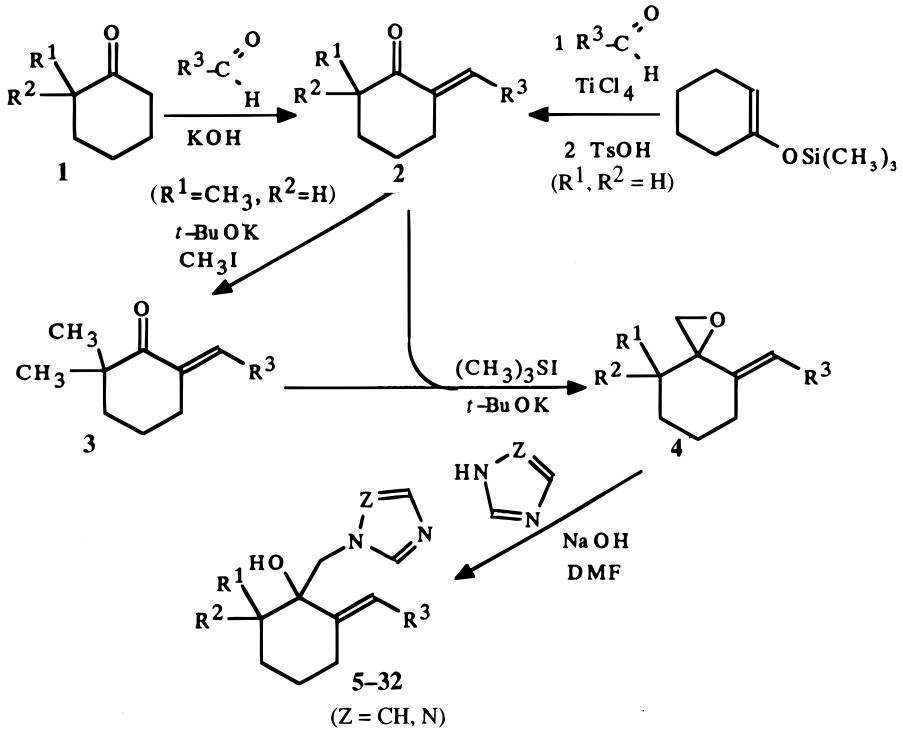


Fig. 1. Synthetic routes to 2-substituted-1-azolylmethyl-6-arylidenecyclohexanol.

Claisen–Schmidt reaction.[3] 2-Benzylidenecyclohexanones were prepared in two steps: reaction of 1-trimethylsilyloxycyclohexene with substituted benzaldehydes in the presence of titanium tetrachloride followed by dehydration of the corresponding aldols with *p*-toluenesulfonic acid in refluxing benzene.[4] Spiro[4.5]decan-5-one was prepared by rearrangement of the corresponding pinacol. This was formed by reduction of cyclopentanone with aluminium amalgam in benzene.[5]

The 2-methyl-6-arylidenecyclohexanones (**2**) were methylated with methyl iodide in the presence of potassium *tert*-butoxide in good yields. The cyclohexanones (**2** and **3**) were transformed to oxiranes (**4**) using the Corey–Chaykovsky reaction.[6,7] The substituted 1-azolylmethyl-6-arylidenecyclohexanols (**5–32**) were produced by interaction between oxiranes (**4**) and 1,2,4-triazole or imidazole.[8–10] Our research group performed this investigation at the same time, but independently from a French group.[11]

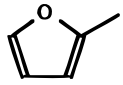
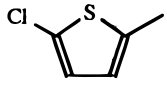
Representative syntheses are described below. Starting materials were obtained from commercial suppliers and were used without further purification. Organic solvents were dried over 4 Å molecular sieves prior to use. Infrared spectra were recorded in liquid film or potassium bromide discs in a Specord Model M-80 infrared spectrometer. NMR spectra were recorded in hexadeuteroacetone or in deuterochloroform on a Varian XL-400 spectrometer at 400 MHz. For all compounds the infrared and NMR spectra were in agreement with the expected structure.

The following sequential procedure for the preparation of compound **18** is typical.

2.1.1 2-(4-Chlorobenzylidene)-6-methylcyclohexanone (**2**)
A mixture of 2-methylcyclohexanone (50 g, 0·45 mol), 4-chlorobenzaldehyde (75·3 g, 0·53 mol) and methanol (110 ml) was stirred for 15 min, after which time aqueous potassium hydroxide (150 g litre^{-1}, 75 ml) was added dropwise. The mixture was refluxed for 2 h and, after cooling, extracted with chloroform (2 × 50 ml) and washed three times with water (3 × 40 ml). After drying over magnesium sulfate and evaporation of the solvents under vacuum, the liquid residues were distilled at reduced pressure (144–150°C/0·01 mm Hg) and recrystallized from isopropanol to furnish 2-(4-chlorobenzylidene)-6-methylcyclohexane as pale yellow needles (67·3 g, 65%), m.p. 63–64°C. δ(deuteroacetone): 1·13 (3H, d, J = 6·7 Hz, CH_3), 1·87–3·04 (7H, series of m, CH cyclohex.), 7·26 (1H, t, J = 6·2 Hz, CH = C), 7·48 (4H, s, ArH). IR (potassium bromide disc) 1670 cm^{-1} (C = 0), 1580 cm^{-1} (CH = C).

2.1.2 2,2-Dimethyl-6-(4-chlorobenzylidene)cyclohexanone (**3**)
The 2-(4-chlorobenzylidene)-6-methylcyclohexanone (17·5 g, 75 mmol) was added to the solution of potassium *tert*-butoxide prepared from potassium (10 g, 0·23 mol) and *tert*-butyl alcohol (250 ml) in an argon atmosphere. The mixture was stirred at room tem-

TABLE 1
Characteristics of 2-Substituted-6-arylidene-1-azolylmethylcyclohexanols

Compound	R^1 [a]	R^2 [a]	R^3 [a]	Z[a]	*m.p.*, (°C)
5	CH_3	CH_3	C_6H_5	N	144–5
6	CH_3	CH_3	C_6H_5	CH	161–2
7	CH_3	CH_3	3-$CH_3C_6H_4$	N	134–5
8	CH_3	CH_3	3-$CH_3C_6H_4$	CH	162–4
9	CH_3	CH_3	4-*i*PrC_6H_4	N	164–5
10	CH_3	CH_3	4-*i*PrC_6H_4	CH	145–7
11	CH_3	CH_3	4-*t*-BuC_6H_4	N	157–9
12	CH_3	CH_3	2-FC_6H_4	N	162–3
13	CH_3	CH_3	2-FC_6H_4	CH	158–9
14	CH_3	CH_3	4-FC_6H_4	N	162–3
15	CH_3	CH_3	4-FC_6H_4	CH	139–40
16	H	H	4-ClC_6H_4	N	Oil
17	CH_3	H	4-ClC_6H_4	N	128–30
18	CH_3	CH_3	4-ClC_6H_4	N	183–4
19	CH_3	CH_3	4-ClC_6H_4	CH	142–3
20	—$(CH_2)_4$—		4-ClC_6H_4	N	214–6
21	CH_3	CH_3O	4-ClC_6H_4	N	206–7
22	CH_3	CH_3O	4-ClC_6H_4	CH	164–5
23	H	H	2,4-$Cl_2C_6H_3$	N	Oil
24	CH_3	H	2,4-$Cl_2C_6H_3$	N	143–4
25	CH_3	CH_3	2,4-$Cl_2C_6H_3$	N	182–3
26	CH_3	CH_3	2,4-$Cl_2C_6H_3$	CH	121–2
27	—$(CH_2)_4$—		2,4-$Cl_2C_6H_3$	N	202–5
28	—$(CH_2)_4$—		2,4-$Cl_2C_6H_3$	CH	212–3
29	H	H	4-BrC_6H_4	N	Oil
30	CH_3	CH_3	4-BrC_6H_4	N	191–3
31	CH_3	CH_3		N	118–20
32	CH_3	CH_3		N	126–7

[a] See Fig. 1.

perature until solution of the ketone was complete (about 15 min), cooled in an ice-salt bath and methyl iodide (62 g, 0·42 mol) was added dropwise. The mixture was stirred under reflux for 1·5 h and the solvent was removed under reduced pressure. Water was added and the crystalline residue was filtered off and washed with water. The fine crystalline precipitate was dried and purified by recrystallization from isopropanol. 2,2-Dimethyl-6-(4-chlorobenzylidene)cyclohexanone was obtained as yellowish crystals (17·5 g, 95%), m.p. 95–96°C. δ(deuteroacetone): 1·11 (6H, s, $CH_3)_2$ *gem.*), 1·72–2·85 (6H, series of m, $(CH_2)_3$ cyclohex.), 7·19 (1H, t, J = 2·3 Hz, CH = C), 7·37 (4H, s, ArH). IR (potassium bromide disc) 1685 cm^{-1} (C = O), 1625 cm^{-1} (CH = C).

*2.1.3 8-(4-Chlorobenzylidene)-4,4-dimethyl-1-oxaspiro[2.5]octane (**4**)*

The mixture of 2,2-dimethyl-6-(4-chlorobenzylidene) cyclohexanone (7·5 g, 30 mmol), trimethylsulfonium iodide (8·6 g, 43 mmol) and dimethylsulfoxide (19 ml) was stirred under argon. After cooling, the solution of potassium *tert*-butoxide (4·3 g, 38 mmol); (prepared from 1·5 g, 38 mmol of potassium and 30 ml of *tert*-butyl alcohol) in dimethylsulfoxide (19 ml) was added and stirring was continued for 15 min. The mixture was cooled in ice-salt bath and then water (90 ml) was added over a period of about 15 min. The mixture was stirred for several minutes and then the ice-salt bath was removed and stirring went on for 30 min. The products were extracted with diethyl ether (2 × 30 ml), washed with water and dried over magnesium sulfate. After evaporation of the solvent, the solid residue was recrystallized from isooctane to give 8-(4-chlorobenzylidene)-4,4-dimethyl-1-oxaspiro[2.5]octane as colourless needles (6·42 g, 81%), m.p. 66–67°C. δ(deuteroacetone): 0·85 (3H, s, CH_3), 0·95 (3H, s, CH_3), 1·57–2·86 (6H, series of m, $(CH_2)_3$ cyclohex.), 2·44–2·99 (2H, AB system, J = 5·4 Hz, CH_2O), 6·44 (1H, t, CH = C), 7·21–

TABLE 2
Fungicidal Activity of 6-Substituted-2-arylidene-1-azolylmethylcyclohexanols

Compound	EC_{50} (*mg litre*$^{-1}$)				
	Sc. sc.[a]	F. g[a]	Rh. s.[a]	H. s.[a]	V. i.[a]
5	2·5	0·40	2·4	3·9	2·7
6	12·7	14·7	4·6	25·5	21·2
7	1·6	0·39	2·4	3·2	0·62
8	10·7	11·0	3·9	20·3	11·7
9	9·0	15·3	10·6	20·8	17·6
10	36·6	33·4	11·5	23·5	15·1
11	16·0	32·7	9·5	50·0	18·6
12	4·6	3·1	3·3	1·7	1·9
13	16·7	5·4	2·9	3·1	10·0
14	1·5	0·95	2·3	1·2	0·94
15	8·9	3·6	3·8	3·2	5·9
16	<1·0	1·3	3·5	1·5	3·9
17	0·46	0·47	3·8	0·15	4·4
18	0·79	2·4	1·0	0·64	0·90
19	14·9	3·9	4·6	2·4	2·0
20	9·7	5·3	46·3	2·4	4·9
21	5·2	3·2	5·7	34·9	14·3
22	38·2	9·2	11·5	16·6	13·1
23	4·6	9·5	7·1	22·7	40·3
24	3·8	10·0	5·2	2·3	1·6
25	5·7	5·3	5·0	1·8	3·7
26	15·7	21·6	19·2	2·9	5·0
27	19·4	16·1	11·7	6·4	12·5
28	13·5	21·6	19·2	2·9	5·0
29	0·68	0·09	4·0	0·30	1·1
30	3·9	0·25	1·9	0·61	0·55
31	9·9	18·3	8·5	23·2	22·4
32	0·82	0·15	2·3	0·16	0·40
Triadimenol	21·9	77·6	104·5	59·0	31·5

[a] Sc. sc.—*Sc. sclerotiorum;* F. g.—*F. graminearum;* Rh. s.—*R. solani;* H. s.—*H. sativum;* V. i.—*V. inaequalis.*

7·33 (4H, AB system, J = 8·4 Hz, ArH). IR (potassium bromide disc) 1590 cm^{-1} (CH = C), 850 cm^{-1} (oxirane).

2.1.4 Typical procedure for synthesis of compounds ***5–32***

The mixture of 8-(4-chlorobenzylidene)-4,4-dimethyl-1-oxaspiro[2.5]octane (6·2 g, 24 mmol), 1,2,4-triazole (1·63 g, 24 mmol) and *N*-methylpyrrolidone (10 ml) was stirred, heated to about 80°C and sodium hydroxide (0·32 g, 8 mmol) and water (0·08 ml, 4·4 mmol) was added. The reaction mixture was heated at about 120°C in an oil bath, and stirring continued for 4 h. After cooling, the mixture was poured into water (50 ml). The precipitate was filtered off, washed with water, dried and purified by crystallization from ethanol. 6-(4-Chlorobenzylidene)-1-(1,2,4-triazol-1-ylmethyl)-2,2-dimethylcyclohexanol was obtained as colourless prisms (4·9 g, 62%), m.p. 183–184°C. δ(deuteroacetone): 0·99 (3H, s, CH_3), 1·15 (3H, s, CH_3), 1·43–2·64 (6H, series of m, $(CH_2)_3$ cyclohex.), 4·19 (1H, s, OH), 4·28–4·97 (2H, AB system, J = 14·3 Hz, CH_2N), 6·19 (1H, s, CH = C), 6·83–7·81 (4H, AB system, J = 8·3 Hz, ArH), 7·70 (1H, s, = CH-N), 8·21 (1H, s, = CH-N). IR (potassium bromide disc) 3200 cm^{-1} (OH), 1650 cm^{-1} (CH = C).

2.3 Biological assays

The compounds were tested for fungicidal activity on *Sclerotinia sclerotiorum* (Lib.) deBary, *Fusarium graminearum* Schwabe, *Rhizoctonia solani* Kuhn. *Helminthosporium sativum* Pammel, King & Bakke and *Venturia inaequalis* Wint. The effect of the chemicals on mycelial radial growth was determined by dissolving them at various concentrations in acetone, and suspending aliquots in potato-glucose agar (PGA) at 50°C to give the required series of concentrations (0·1–150 mg ml^{-1}). The final acetone concentration of both fungicide-containing and control samples was 10 ml litre^{-1}. Petri dishes containing 10 ml of the agar medium were inoculated by placing 6-mm fungus-coated discs upside down on the agar surface. Plates were incubated at 25°C and radial growth was measured after three days. The EC_{50} was calculated for each fungicide.

3 RESULTS

The results of the tests are given in Table 2. Most compounds showed good activity. Triazolylmethylcyclohexanols appear to be more potent than imidazole analogues.

4 DISCUSSION

The substituted azolylmethylcyclohexanols prepared showed strong activity on five fungi. Examination of Table 2 shows that fungicidal activity depends strongly on both the arylidene fragment in the 6-position and the groups in the 2-position of the cyclohexanol. Products **7, 14, 16–19, 29, 30** and **32** showed very good activity against all the tested fungi. **12** and **25** were active on *H. sativum*, and **12** and **24** inhibited mycelial growth of *V. inaequalis* significantly. From this classification, certain structure–activity relationships can be deduced.

Comparison of the structures of lanosterol and 2-substituted 6-arylidene-1-azolylmethylcyclohexanols by computer modelling[12] in Fig. 2 suggests that the benzylidene fragment of our compounds models the A-ring of lanosterol. On the other hand, the *gem*-dimethyl group in the 2-position of cyclohexanol is similar to the fork of the C-13 atom of the sterol, so that the cyclohexanol

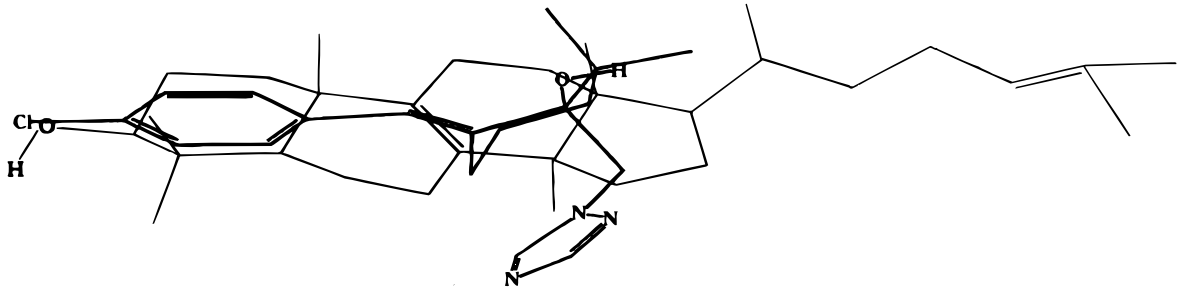


Fig. 2. Comparison of the structures of Compound **18** and lanosterol.

ring can perhaps occupy a similar position as the D-ring of lanosterol. This suggested arrangement of the 2-substituted-6-arylidene-1-azolylmethylcyclohexanol in the active site of P-450 oxidase supports the explanation of the inhibition of sterol biosynthesis by interaction of triazole ring with the active centre of the enzyme. Inspection of the overlay suggests that at least one methyl in the 2-position of the cyclohexanol is required for good overlap with the methyl on the 13-carbon (and therefore for good activity), but that a second methyl may not be necessary. This is supported by comparison of the activities of **16, 17** and **18**. The activity of the monomethyl compound **17** is approximately the same as that of the *gem*-dimethyl compound **16.** However, the picture is confused by **19,** which lacks any methyls, but which is at least as active as its *gem*-dimethyl analogue **30.** Clearly more work will be needed to understand these structure–activity relationships fully. When the *gem*-dimethyl group was replaced with a tetramethylene chain, as in **20,** the activity was greatly reduced, probably because of the steric hindrance of this structural unit. Replacement of the methyl group in **18** by a methoxy group (**21**) caused a great reduction of fungicidal activity.

The influence of the benzylidene group on C6 of the azolylmethylcyclohexanol is not so obvious. In general, compounds with a single halogen substituent in the 4-position are very active, e.g. **14, 18** and **30,** while addition of a second halogen in the 2-position reduces activity. A bulky alkyl group in the 4-position also reduces activity. This trend can be explained in a number of ways. For example, the spatial disposition of the halogen atom in the 4-position of the azolylmethylcyclohexanols coincides with the electronegative hydroxyl group of C-3 of lanosterol. The 3-methyl compound is surprisingly active. This anomalously high activity can be rationalized by the similarity of the 3-methylbenzylidene fragment to the C-4 methyl group in lanosterol. The corresponding 4-methyl compound was not available for comparison.

In conclusion, a number of effective chemical agents for the control of *Sclerotinia sclerotiorum*, *Fusarium graminearum*, *Rhizoctonia solani*, *Helminthosporium sativum* and *Venturia inaequalis* have been identified. Certain of the chemical structures investigated have been selected for more detailed biological evaluation. The high activity of our compounds on the fungi tested can be explained by the similarity between lanosterol and the substituted azolylcyclohexanols. These compounds will be further studied as potential fungicides.

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REFERENCES

1. Davidse, L. C. & de Waard, M. A. Systemic fungicides. In *Advances in Plant Pathology*, Vol. 2, ed. D. S. Ingram & P. H. Williams. Academic Press, London, San Francisco, New York, Montreal, Sydney, Tokyo, 1984, pp. 214–20.
2. Buechel, K. H., Kramer, W., Meiser W. & Grewe, F., Chemistry and properties of flutrimazole and related fungicides of the azole class. *8th Int. Cong. Plant Prot.* **3** (1975) 111–18.
3. Johnson, W. S., Introduction of the angular methyl group. The preparation of *cis*- and trans-9-methyldecalone-1. *J. Am. Chem. Soc.*, **65** (1943) 1317–24.
4. Mukaiyama, T., Banno, K. & Narasaka, K., New cross-aldol reactions. Reactions of silyl enol ethers with carbonyl compounds activated by titannium tetrachloride. *J. Am. Chem. Soc.*, **96** (1974) 7503–9.
5. Elagina, N. V. & Zelinsky, N. D., Preparation of pinacols of mixed types by simultaneous reduction of two ketones. *Doklady Akad. Nauk SSSR*, **71** (1950) 293–4.
6. Corey, E. J. & Chaykovsky, M., Dimethylsoxosulfonium methylide ($(CH_3)_2SOCH_2$) and dimethylsulfonium methylide ($(CH_3)_2SCH_2$). Formation and application to organic synthesis. *J. Am. Chem. Soc.*, **87** (1965) 1353–64.
7. Franzen, V. & Driesen, H-E., Umsetsung von Sulfonium-Yliden mit polaren Doppelbindungen. *Ber.*, **96** (1963) 1881–90.
8. Research Institute of Plant Protecting Chemicals & Kemira AU, USSR Patent 1 838 304, 1993.
9. Kureha Kagaku Kogyo Kabushiki Kaisha, EP 0 267 778, 1988.
10. Kovalenko, L. V., Popkov, S. V., Bobylev, M. M., Molchanov, O. Yu., Krimer, M. Z., Tashchi, V. P. & Putsykin, Yu. G., The synthesis and the fungicidal activity of 2-substituted 6-benzyliden-1-azolymethylcyclohexanols. *Agrokhimiya*, **7–8** (1994) 76–81.
11. Rhone-Poulenc Agrochimie, EP 0 378 953, 1990.
12. Marchington, A. F., Role of computergraphics in the design of plant protection chemicals. *10th Int. Cong. Plant. Prot.*, **1** (1983) 201–8.